Effects of sustained mild hypothermia on neurocognitive function after coronary artery bypass surgery: A randomized, double-blind study

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Supplemental material is available online.

Objective: Neurocognitive deficits occur frequently in patients undergoing cardiac surgery and may be caused, in part, by ischemic cerebral injury. Cerebral hypothermia has been proposed as a neuroprotective strategy to reduce ischemic injury in animal studies, in postcardiac arrest, and during cardiac surgery. We sought to evaluate the effects of sustained mild intraoperative hypothermia, without rewarming, on neurocognitive function after coronary artery bypass surgery.

Methods: Patients (aged ≥ 60 years) undergoing non-urgent coronary surgery were randomized to an intraoperative nasopharyngeal temperature of 34°C (hypothermic; n = 133) or 37°C (normothermic; n = 134), maintained using water-circulating thermal control pads. No active rewarming was used. Transcranial Doppler was used intraoperatively to monitor middle cerebral artery emboli. Neuropsychometric testing, consisting of a battery of 16 tests, was performed by blinded observers preoperatively, before discharge, and at 3 months, and tests were divided into 4 cognitive domains. A deficit was prospectively defined as a 1 standard deviation decrease in individual scores from baseline in 1 or more domains.

Results: The number of intraoperative cerebral emboli was similar between the control and the treated groups (188 [115–331] vs 182 [100–305], $P = .71$). At discharge, neurocognitive deficits were present in 45% of control patients and in 49% of treated patients ($P = .49$) and at 3 months decreased to 8% in control patients and 4% in treated patients ($P = .28$). There was no correlation between the total number of cerebral emboli and the occurrence of neurocognitive deficits ($r = -0.01$; $P = .88$). Hypothermic patients demonstrated trends toward reduced intensive care unit stay (1.4 ± 1.0 days vs 1.2 ± 0.7 days, $P = .06$) and increased chest tube output (655 ± 327 mL/24 h vs 584 ± 325 mL/24 h, $P = .09$).

Conclusions: Mild intraoperative hypothermia has no major adverse effects but does not decrease the incidence of neurocognitive deficits in patients undergoing coronary artery bypass surgery. In the absence of rewarming and cerebral hyperthermia, sustained mild hypothermia does not improve cognitive outcome.

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This study was supported by a grant from the Canadian Institutes for Health Research. Clinical Trial Registration: ISRCTN59467488.

Read at the Eighty-seventh Annual Meeting of The American Association for Thoracic Surgery, Washington, DC, May 4-9, 2007.

Received for publication March 20, 2007; revisions received July 18, 2007; accepted for publication Aug 15, 2007.

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J Thorac Cardiovasc Surg 2007;134:1443-52

0022-5223/$32.00

doi:10.1016/j.jtcvs.2007.08.016

Postoperative cognitive deficits (POCDs), defined as impairments in memory, attention, and psychomotor function, are observed in 30% to 80% of patients after cardiac surgery.[1] These deficits may be associated with distress for patients and families, delayed return to work and normal functioning, prolonged

Abbreviations and Acronyms
CPB = cardiopulmonary bypass
HITS = high-intensity transit signals
ICU = intensive care unit
POCD = postoperative cognitive deficit
SF-12 = Short Form Health Survey [12 items]

CSP

hospital stay, and reduced quality of life.[2] Most important, the occurrence of POCDs has repeatedly been associated with late cognitive decline.[3-5] Although a number of strategies have been proposed to reduce the occurrence of POCDs, no clear benefits have been demonstrated by clinical studies to date.

Evidence from animal studies has clearly demonstrated a large protective effect of mild hypothermia (2°C–5°C decrease in brain temperature) in the setting of global cerebral ischemia followed by reperfusion.[6,7] This neuroprotective effect of mild hypothermia has also been observed in patients with out-of-hospital cardiac arrest.[8] These studies have encouraged us to test the hypothesis that mild hypothermia minimizes neurologic injury in patients undergoing cardiac surgery.

The Warm Heart study first demonstrated the safety and potential benefits of normothermic coronary artery surgery with respect to myocardial preservation with no detrimental effects on neurologic outcome.[9] Subsequent clinical trials have yielded conflicting results regarding the neuroprotective effects of hypothermia.[10] In the majority of these studies, the duration of exposure to hypothermia was short and the treated (hypothermic) patients were often actively rewarmed with brain temperatures often exceeding 38°C, which may have adverse effects on neurocognitive outcome.[11]

We previously reported that, in patients undergoing coronary artery bypass surgery who were cooled to 32°C during cardiopulmonary bypass (CPB), rewarming to 34°C compared with 37°C was associated with a 23% reduction in the incidence of POCDs ($P = .04$).[12] It was unclear whether the hypothermic group had benefited from a neuroprotective effect of mild hypothermia per se or from the lesser extent and rate of rewarming. Thus, in this study, we evaluated the neuroprotective effects of sustained mild hypothermia (34°C) maintained throughout the intraoperative period with no rewarming compared with effects of normothermia (37°C) in a similar population. We hypothesized that sustained mild hypothermia would lead to an even greater neuroprotective effect by extending the period of protection and avoiding any injury associated with rewarming on CPB.

Materials and Methods

Patient Population

Between September 2000 and December 2004, patients aged 60 years or more who were scheduled to undergo non-urgent coronary artery surgery at the University of Ottawa Heart Institute were asked for informed consent for enrollment in this trial, which was approved by our institutional review board. Patients with known neurologic deficits (previous stroke, history of Parkinson disease, Canadian Neurological Scale[13] score < 11.5, or abnormal Modified Mini-Mental State scores) and serum creatinine greater than twice the normal level (normal range, men: 62-106 μmol/L; women: 35-88 μmol/L) were excluded. Patients undergoing repeat cardiac surgery were initially included, but soon after study initiation the selection criteria were modified to exclude these patients. Thus, only 4 patients with a history of cardiac surgery were included in the study.

Intraoperative Protocol and Randomization

Anesthesia induction and monitoring were performed as previously reported.[14] After the induction of anesthesia, a temperature probe was placed in the nasopharynx, and this temperature was monitored and controlled throughout the intraoperative period. Bladder temperature was used as an indicator of visceral temperature.

Eligible and consenting patients were equally assigned to hypothermia or normothermia by using a computer-generated randomization list. Randomization was performed 30 minutes before the operation in blocks of 8 and stratified according to age more than 75 years. Treatment assignment was concealed in opaque, sealed envelopes that were assigned sequentially as patients were enrolled, according to age block.

Patients were unaware of the treatment assignment, which was not concealed from the clinical staff. Patients in the normothermic group were warmed with a forced-air heating blanket for 15 to 30 minutes before entering the operating room. Upon the patient's arrival to the operating room, high-efficiency thermal pads were applied to the patient's back and posterior aspect of the upper leg. The pads were connected to a water-circulating thermal control system (Arctic Sun; Medivance Corporation, Louisville, Colo), and cooling to 34°C or warming to 37°C was begun. Patients' nasopharyngeal temperatures were kept as close as possible to 37°C or 34°C throughout the intraoperative period. CPB was performed via an ascending aortic cannula and a 2-stage right atrial cannula using membrane oxygenators and 43-μm arterial line filters (Cobe Cardiovascular, Arvada, Colo) maintaining a nonpulsatile flow at 2.5 to 2.8 L/min/m^2. Mean arterial pressure was maintained between 50 and 80 mm Hg using phenylephrine or isoflurane. Blood gases were not temperature corrected. The heater/cooler was used only to make small corrections in temperature during CPB; the temperature of blood leaving the oxygenator was monitored and recorded and was not allowed to exceed 37.5°C or 34.5°C in the normothermic and hypothermic groups, respectively. After application of the aortic crossclamp, cardiac arrest was induced and maintained with antegrade cold crystalloid or blood cardioplegia.

Nasopharyngeal temperatures were kept constant at 34°C or 37°C until arrival to the intensive care unit (ICU). In the ICU, forced-air warming blankets were applied. Postoperative care, including blood product use, reexploration for bleeding, extuba-

tion, and ICU discharge, was conducted according to protocols previously described.[14]

Intraoperative Transcranial Doppler

Transcranial Doppler examinations were performed as previously described.[15] Briefly, once the patient was asleep, bilateral 2-MHz pulsed-wave Doppler probes (sample volume: 10 mm) were secured on the temporal area using an adjustable headband (Marc 600; Spencer Technologies, Seattle, Wash) for continuous monitoring of the middle cerebral artery flow velocities. A dual-gated (separation: 5 mm), pulsed-wave transcranial Doppler system (DWL, Sipplingen, Germany,) recorded (dynamic range: 60 dB, overlapping: 58%), filtered (100 Hz), and stored both the Doppler waveforms and embolic signals (intensity threshold: 9 dB).

An ultrasonographer (R.A.R.), who was unaware of the cognitive findings and temperature treatment, reviewed the Doppler recording classified high-intensity transit signals (HITS) as true or equivocal on the basis of the acoustic and Doppler spectra characteristics of the embolus and the time delay caused by the embolus traveling between the 2 sample volumes.[16] Artifacts and equivocal HITS were not included in the final analysis. The interobserver agreement in our center for discriminating between true HITS and artifacts using these Doppler characteristics has been reported to be excellent.[15] The total count of HITS for each patient was the sum of bilateral counts recorded from the time of aortic cannulation until the removal of the aortic cannula after CPB. Only patients with successful bilateral Doppler recordings of the middle cerebral artery were included in the final analysis.

Neuropsychometric Evaluation

Neurologic status was assessed on the first postoperative day using the Canadian Neurological Scale.[13] The National Institutes of Health Stroke Scale was administered preoperatively and 1 week and 3 months postoperatively.

We used conventional psychometric tests[17] with empirically derived reliability and validity data, and included the core tests recommended by a consensus conference on assessment of neurobehavioral outcomes after cardiac surgery.[18] Neurocognitive testing was performed at all time points under similar conditions and, whenever possible, by the same evaluator. Alternate forms were used to reduce learning effects. To optimize the reliability of the neuropsychometric evaluation, the psychometrists were trained and periodically audited by the same neuropsychologist. All patients were ambulating and fit for discharge at the time of postoperative assessment.

Learning efficiency and memory consolidation were evaluated with the Rey Auditory Verbal Learning Test. Psychomotor speed and dexterity, known to be a sensitive indicator of the presence of generalized brain dysfunction, was measured by the Trails A and B, Grooved Pegboard, and Symbol Digit Modalities Test (oral administration). Attentional capacity and control were evaluated using the revised Wechsler Adult Intelligence Scale Digit Span. To further evaluate this domain, we added the Mental Control Subtest of the Wechsler Memory Scale-III, in which the score reflects both speed and accuracy. Letter and Category Fluency was used to assess the speed and flexibility of verbal thought processes. To further evaluate the motor domain, finger tapping was evaluated on both hands.

Pre- and postoperative measures of mood (Geriatric Depression Scale) and anxiety (State-Trait Anxiety Inventory) were also recorded. The total battery required 60 minutes to administer. The Short Form Health Survey[19] (SF-12) (QualityMetric Inc, Lincoln, RI) was administered preoperatively and 3 months postoperatively to assess health-related quality of life.

Safety End Points

Safety end points were recorded as previously described[14] both during and after surgery and included nasopharyngeal, bladder, and oxygenator outlet temperatures, use of blood products, bleeding from chest tubes during 24 hours, use of inotropic and vasopressor drugs, time on CPB, and aortic crossclamp time. Furthermore, time until extubation, days in the ICU, and days in the hospital were noted. Myocardial infarction was defined as the appearance of new Q waves more than 0.04 seconds in duration in at least 2 contiguous leads. Creatine kinase was measured on the morning after surgery. Troponin T was determined if the total creatine kinase was greater than 800 U/L. Chest and leg wound infections were documented by the infection control service using established definitions.[20]

Statistical Analysis

Psychometric test results were analyzed both as continuous and dichotomous outcomes. Individual psychometric test scores yielded continuous measures repeated at 3 time points (preoperatively and 1-week and 3-month follow-ups). As such, individual scores were analyzed using mixed models to account for correlated repeated-measures data. The mixed models used an unstructured covariance matrix, and the model included a term for treatment and time-by-treatment interactions. No other covariates were added to the model.

To facilitate the categoric analysis, the psychometric tests were combined into 4 cognitive domains using factor analysis with orthogonal rotation as described by Newman and coworkers.[4] This method reduced the individual test scores into 4 factors that were uncorrelated and accounted for 80% of the variance present in the test battery and approximately corresponded to the following areas of cognitive functioning: verbal memory, psychomotor speed and dexterity, attention, and motor function. The scores were adjusted so that an increase in score always indicated better performance, and a composite score, intended to represent overall cognitive performance, was formed by summing the 4 individual factors (composite cognitive index). A patient was deemed to have had a cognitive deficit if 1 or more factor scores decreased by at least 1 standard deviation. A secondary analysis was performed using the reliable change index methodology to account for practice effects. A cohort of 75 nonsurgical control subjects with coronary artery disease were tested at the same intervals as well as patients, and this information was used to adjust for practice effects in the study patients as described by Rasmussen and colleagues.[21]

Data are presented as mean ± standard deviation or median (interquartile range). Continuous variables were compared by using unpaired *t* tests if normally distributed or the Wilcoxon rank–sum test for non-normally distributed variables. Categoric data, including the primary end point of POCD incidence, were compared by using a chi-square test. The Fisher exact test was used when an expected cell count was less than 5. The primary analysis

TABLE 1. Baseline demographics

Characteristic	Normothermic (n = 133)	Hypothermic (n = 134)	P
Age	69.3 ± 6	68.2 ± 6	.12
Male sex	116 (87)	119 (85)	.46
Education level			.72
Less than Grade 9	18 (13)	16 (12)	
Grades 9-12	56 (42)	63 (47)	
Postsecondary	59 (44)	55 (41)	
Diabetes			.12
None	87 (65)	87 (65)	
Diet-controlled	5 (4)	10 (8)	
Oral medications	37 (28)	27 (20)	
Insulin	4 (3)	10 (8)	
LV dysfunction	16 (12)	10 (7)	.21
CCS angina class			.15
I	4 (3)	13 (10)	
II	32 (24)	33 (25)	
III	68 (51)	63 (47)	
IV	29 (22)	25 (19)	
NYHA functional class			.66
I	120 (90)	125 (93)	
II	9 (7)	6 (5)	
III	4 (3)	3 (2)	
Serum creatinine (μmol/L)	91.3 ± 17	93.7 ± 20	.29
Peripheral vascular disease	22 (17)	19 (14)	.59
Carotid disease	10 (8)	6 (5)	.29
Urgent surgery	26 (20)	28 (21)	.78
Redo surgery	3 (2)	1 (1)	.61

LV, Left ventricle; *CCS*, Canadian Cardiovascular Society; *NYHA*, New York Heart Association. Continuous data are presented as mean ± standard deviation or median (interquartile range); *t* tests or Wilcoxon rank–sum tests are used for continuous variables depending on normality; the chi-square or Fisher exact test is used for categoric variables.

was by treatment group (normothermia or hypothermia), with no exclusions.

Sample Size

A prospectively performed sample size calculation indicated that the sample size of 300 patients provides 80% power (with $\alpha = 0.05$) to detect a 27% difference in incidence of POCDs given a rate of 60% in the control group. The study was terminated after 267 patients had been randomized as funds were exhausted.

Results

Figure E1 summarizes the patient recruitment and follow-up information. Of 3196 patients screened, 613 met the inclusion and exclusion criteria, 286 gave informed consent, and 267 were randomized. Predischarge neurocognitive testing was completed in 255 patients (96%), and 3-month testing was completed in 236 patients (88%).

Baseline characteristics were similar between groups (Table 1). Intraoperative and postoperative nasopharyngeal temperatures are depicted in Figure 1. The target temperature was achieved and maintained in all patients throughout the operative period. By the time of aortic cannulation (arguably the earliest intervention with the potential for cerebral insult), the nasopharyngeal temperatures were significantly lower in the hypothermic group. At the time of sternal closure, the nasopharyngeal temperature was 36.8°C ± 0.3°C in the normothermic group and 34.2°C ± 0.2°C in the hypothermic group. After arrival to the ICU, the hypothermic patients took an average of 3.4 ± 1.1 hours to reach 36°C. Ninety percent of patients had reached a temperature of 36°C 4 hours after arrival to the ICU. Table 2 shows the intraoperative and postoperative outcomes.

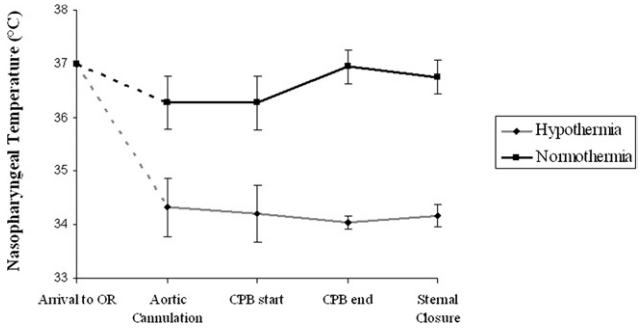

Figure 1. Intraoperative nasopharyngeal temperature of study patients (mean ± standard deviation). *OR,* Operating room; *CPB,* cardiopulmonary bypass.

Safety End Points

The patients assigned to hypothermia demonstrated a trend toward reduced ICU stay ($P = .06$). In-hospital stay, however, was similar between groups. There was a trend toward a small increase in chest tube output of 71 mL ($P = .09$). Reexploration rates for bleeding and blood transfusion rates were similar between groups (31% vs 39%, $P = .14$). Hypothermic patients had lower serum creatine kinase levels 6 hours after surgery ($P < .001$). Troponin T levels were measured in all patients who had creatine kinase levels greater than 800 U/L and were similar between groups. The incidence of clinical and electrocardiographically diagnosed myocardial infarction was also similar between groups.

Neurocognitive Outcome

Table 3 depicts the results of the neurocognitive tests and factor-based analyses. Overall, there was a decline in performance on neurocognitive tests at the predischarge time point with some recovery at 3 months. However, time-by-treatment interactions (indicating differential changes over time between groups) were nonsignificant for all tests except for Digits Backward ($P = .008$), which demonstrated improved scores for hypothermic patients both at discharge

TABLE 2. Intraoperative and postoperative data

Characteristic	Normothermic (n = 134)	Hypothermic (n = 133)	P
CPB time (min)	80.5 ± 23.4	77.2 ± 22.5	.23
Cardiac anoxia time (min)	47.2 ± 14.9	45.5 ± 16.2	.39
No. of grafts	3.1 ± 0.1	2.9 ± 0.1	.07
In-hospital mortality (%)	1 (1)	3 (2)	.37
Focal neurologic deficits (%)	0 (0)	1 (1)	1.0
Encephalopathy (%)	4 (3)	4 (3)	1.0
Creatine kinase	660 ± 480	496 ± 255	<.001
Troponin T	0.59 ± 0.39	0.51 ± 0.34	.23
Reopening for bleeding (%)	3 (2)	3 (2)	1.0
Time to extubation (h)	8.1 (5.9–11.6)	8.6 (6.8–12.3)	.49
ICU length of stay (d)	1.03 (0.92–1.67)	0.98 (0.90–1.13)	.06
In-hospital length of stay (d)	5 (5–7)	6 (5–7)	.94
Chest tube output (mL)	584 ± 325	655 ± 327	.09
Patients requiring blood products (%)	41 (31)	52 (39)	.14
Perioperative atrial fibrillation (%)	49 (39)	44 (34)	.43
Wound infections (%)	8 (6)	4 (3)	.38

CPB, Cardiopulmonary bypass; *ICU*, intensive care unit. Continuous data are presented as mean ± standard deviation or median (interquartile range); *t* tests or Wilcoxon rank–sum tests are used for continuous variables depending on normality; chi-square or Fisher exact test is used for categoric variables.

and at 3-month follow-up. A significant difference favoring hypothermia was also seen in the attention domain ($P = .03$), likely driven by the difference in the Digits Backward test result. However, after adjustment for multiple comparisons these differences were not statistically significant.

Defined dichotomously, POCDs were identified in 45% of normothermic patients and 49% of hypothermic patients at discharge ($P = .49$). At 3 months, only 8% of normothermic patients and 4% of hypothermic patients demonstrated neurocognitive deficits ($P = .28$) (Table 4). Secondary analyses, performed using the reliable change index, showed a similar incidence of POCDs at discharge with no significant differences between groups (43% vs 48%, hypothermic vs normothermic, $P = .49$).

Cerebral Emboli

Intraoperative transcranial Doppler recordings were successfully obtained in 188 patients (70%). The total number of HITS was similar between groups (Table 4). Furthermore, there was no significant correlation between the total number of HITS and the composite cognitive index, a continuous measure of cognitive function (Spearman $r = -0.01$, $P = .88$).

Quality of Life

Quality of life, evaluated using the SF-12,[19] was similar between groups, both in the Physical and Mental domains, at baseline and at 3 months. There was a significant increase in self-reported quality of life after surgery. Compared with those of patients at baseline, patients with neurocognitive deficits at discharge demonstrated a smaller improvement in the Mental component of the SF-12 ($P = .03$) but not in the Physical component ($P = .70$) at 3 months.

Discussion

We sought to determine whether sustained mild hypothermia with no rewarming, compared with normothermia, could reduce POCDs in patients undergoing coronary artery bypass grafting. In this randomized patient- and assessor-blinded study, we demonstrated that mild hypothermia (34°C) sustained throughout the intraoperative period does not result in any major adverse events. We found, however, that the incidence of POCDs was similar between the normothermic and hypothermic groups. The number of cerebral emboli, detected using transcranial Doppler examination, was also similar between groups, and there was no correlation between the number of cerebral emboli and neurocognitive outcome. Last, self-reported quality of life was similar between normothermic and hypothermic patients. Patients with POCDs at discharge reported less improvement in the Mental component of the quality of life scores 3 months postoperatively.

In a previous study,[12] we examined the effect of hypothermia in cardiac surgical patients who were cooled to 32°C and then randomized to rewarming (avoiding cerebral hyperthermia) to 34°C or 37°C. We found that mild hypothermia in this setting led to a statistically significant and clinically relevant 23% reduction in the early incidence of POCDs, as well as a highly significant and consistent difference in performance on the grooved pegboard test at 3 months. We hypothesized that sustained mild hypothermia

TABLE 3. Neuropsychometric test results

	Normothermia			Hypothermia		
		Change from preoperative			Change from preoperative	
	Preoperative	1 wk	3 mo	Preoperative	1 wk	3 mo
Factor 1: Verbal Memory	−0.003 ± 1.06	−0.35 ± 0.76	−0.22 ± 0.81	0.003 ± 0.94	−0.44 ± 0.84	−0.19 ± 0.73
RAVLT: Total (TI-T5)	38.4 ± 9.6	−2.2 ± 7.8	−1.0 ± 7.6	37.8 ± 9.2	−2.3 ± 7.4	0.3 ± 7.1
Trial 6	7.2 ± 3.2	−1.0 ± 2.5	−0.4 ± 2.6	7.2 ± 2.9	−1.0 ± 2.7	−0.1 ± 2.4
Trial 7 (delayed recall)	6.9 ± 3.2	−1.5 ± 2.7	−0.5 ± 2.4	6.9 ± 3.1	−1.6 ± 2.8	−0.4 ± 2.5
Retention	−2.6 ± 2.0	−0.7 ± 2.6	−0.3 ± 2.7	−2.5 ± 2.0	−0.9 ± 2.5	−0.5 ± 2.4
Recognition	12.7 ± 2.5	−0.7 ± 2.2	−0.4 ± 2.2	12.6 ± 2.1	−1.0 ± 2.5	−0.2 ± 1.9
Factor 2: Attention*	0.051 ± 0.93	−0.065 ± 0.58	0.072 ± 0.54	−0.05 ± 1.06	0.01 ± 0.63	0.28 ± 0.54
Digback*	6.3 ± 2.1	−0.8 ± 1.6	−0.3 ± 1.7	6.1 ± 2.1	−0.4 ± 1.6	0.5 ± 1.9
Digfor	9.6 ± 2.0	−0.3 ± 1.9	0.3 ± 1.8	9.7 ± 2.2	−0.1 ± 2.0	0.3 ± 1.7
WMS Mental Control	24.7 ± 5.2	−0.8 ± 3.8	0.7 ± 4.0	24.2 ± 5.5	−0.8 ± 4.1	1.5 ± 3.3
Letter fluency	32.2 ± 12.4	−0.8 ± 7.8	1.0 ± 8.1	31.7 ± 12.1	−0.9 ± 8.7	2.6 ± 7.2
Category fluency (animal)	18.5 ± 4.9	−1.9 ± 4.3	−0.0 ± 4.2	18.4 ± 4.7	−1.6 ± 4.2	0.0 ± 3.9
Factor 3: Psychomotor Speed	0.000 ± 1.0	−0.58 ± 0.90	0.16 ± 0.48	0.000 ± 1.0	−0.59 ± 0.82	0.22 ± 0.47
Trails A	40.2 ± 12.3	3.7 ± 14.4	−1.4 ± 11.9	41.9 ± 14.8	2.5 ± 13.8	−4.0 ± 12.3
Trails B	103.3 ± 43.3	7.7 ± 39.7	−7.8 ± 35.5	105.6 ± 45.0	13.5 ± 43.2	−11.7 ± 29.0
Pegtime (dominant hand)	91.1 ± 24.4	15.1 ± 24.9	−2.0 ± 14.8	90.1 ± 20.5	15.0 ± 22.0	−4.0 ± 13.4
Pegtime (nondominant hand)	100.1 ± 28.3	18.5 ± 27.9	−3.5 ± 13.7	99.2 ± 26.6	16.6 ± 26.6	−4.3 ± 18.2
SDMT	43.1 ± 9.7	−4.6 ± 6.7	1.8 ± 6.7	42.9 ± 9.4	−5.0 ± 7.3	2.1 ± 5.3
Factor 4: Motor	−0.016 ± 1.01	−0.093 ± 0.74	0.17 ± 0.73	0.016 ± 1.0	−0.091 ± 0.65	0.059 ± 0.55
Finger Tapping (dominant hand)	46.8 ± 8.1	−1.7 ± 6.4	1.6 ± 5.8	46.9 ± 7.9	−1.6 ± 5.7	1.3 ± 4.9
Finger Tapping (nondominant hand)	43.6 ± 7.3	−1.6 ± 5.4	1.2 ± 5.3	43.9 ± 7.4	−1.7 ± 4.5	0.6 ± 3.7

RAVLT, Rey Auditory Verbal Learning Test; *WMS*, Wechsler Memory Scale; *SDMT*, Symbol Digit Modalities Test. Scores for individual neuropsychometric tests and the 4 factors at baseline and changes at 1 week and 3 months are depicted in the normothermic and hypothermic groups. Only the Digit Span Backward test and Factor 2: Attention demonstrated significant differences between groups. 1 wk = early postoperative score-preoperative score; 3 mo = 3-mo score-preoperative score; Pegtime = grooved pegboard; Digfor = digit span forward; digback = digit span backward. For timed measures (Trails A, Trails B, Pegtime), a longer time indicates poorer performance. For all other tests, increased score indicates improved performance. All scores presented as mean ± standard deviation. *$P < .05$ mixed model evaluating time-by-treatment interaction.

would lead to an even greater neuroprotective effect by extending the period of protection and avoiding any injury associated with rewarming on CPB. We did not detect a significant difference in neuropsychologic outcome between groups in this study. Given the similar study conditions, patient populations, and outcome measures between the 2 studies, the absence of benefit suggests that mild hypothermia per se was not responsible for the lower incidence of POCDs in the earlier study. Rewarming (32°C–37°C during a period of 10–15 minutes), even in the absence of hyperthermia, was likely responsible for worse neurocognitive outcome in the normothermic group in the previous study (Figure 2).

Temperature monitoring and management practices during CPB remain variable across surgeons, anesthesiologists, perfusionists, and institutions,[22] largely because of the absence of adequately powered randomized clinical trials to provide guidance in this area. A recent evidence-based review that discussed temperature management during CBP practices suggested limiting the arterial line temperature to 37°C to avoid cerebral hyperthermia as a class IIa recommendation.[10] However, no specific recommendations were given with respect to hypothermia and rewarming. The findings of this study challenge the conventional thinking that mild intraoperative hypothermia in cardiac surgical patients is neuroprotective. Furthermore, taken together, evidence from our 2 clinical trials suggests that rapid rewarming is associated with increased neurocognitive deficits. Thus, the temperature at which patients are maintained is less important as long as cerebral hyperthermia and rapid rewarming are avoided. It is important to note that these data cannot be generalized to the setting of mild hypothermia in the context of ischemic brain injury caused by atheromatous emboli or hypoperfusion. Should the clinician decide to use mild hypothermia to reduce ischemic injury on the basis of laboratory evidence and its efficacy in the setting of cardiac arrest, our data suggest that it is without serious adverse effects in patients who are at low risk of bleeding.

Our previously published interim safety analysis demonstrated the safety of deliberate, sustained, mild hypothermia in cardiac surgery patients.[14] The final analysis of safety end points in these patients corroborates our previous report. The incidence of clinically significant bleeding was similar between groups, as suggested by equivalent rates of reexploration and blood product use. Chest tube losses were

TABLE 4. Effect of mild hypothermia on the incidence of postoperative cognitive deficits, intraoperative cerebral emboli, and quality of life

Characteristic	Normothermic	Hypothermic	*P*
POCDs at discharge	45%	49%	.49
POCDs at 3 mo	8%	4%	.28
Transcranial Doppler HITS (n = 188)	188 (115–331)	182 (100–305)	.71
SF-12: Baseline			
Physical Component Score	35.4 ± 10.3	34.8 ± 9.4	.66
Mental Component Score	52.8 ± 8.0	52.4 ± 9.2	.68
SF-12: 3 mo			
Physical Component Score	42.3 ± 10.4	44.0 ± 9.1	.22
Mental Component Score	54.1 ± 7.8	55.2 ± 7.0	.29

POCD, Postoperative cognitive deficit; *HITS,* high-intensity transit signals; *SF-12,* Short Form Health Survey [12 items]. *T* tests or Wilcoxon rank-sum tests are used for continuous variables depending on normality, and chi-square or Fisher exact test is used for categoric variables.

nonsignificantly higher in hypothermic patients by approximately 70 mL per patient. Surprisingly, the length of stay in the ICU was slightly shorter in hypothermic patients, a trend that did not reach statistical significance. The incidence of perioperative myocardial infarction and serum troponin levels were both similar between groups. We found that the 3-month incidence of POCDs was higher in the normothermic patients compared with hypothermic patients (8% vs 4%, respectively, $P = .28$). Although this represents a relative risk reduction of 50% with hypothermia, it is only an absolute risk reduction of 4%, and this study was not powered to detect such a small difference at the 3-month follow-up. Thus, deliberate sustained intraoperative and perioperative hypothermia and sustained normothermia are both safe in this low-risk population of patients undergoing coronary artery bypass grafting.

Although atherosclerotic macroemboli arising from the ascending aorta are clearly a source of postoperative stroke, the relationship between intraoperative cerebral microemboli and POCDs continues to be debated. The presence of fat emboli in the brain has been demonstrated at autopsy after cardiac surgery.[23,24] In our study, there was no difference in the number of HITS between the hypothermic and normothermic groups. More important, the total number of HITS did not correlate with postoperative neurocognitive function in the total cohort of 188 patients with high-quality transcranial Doppler recordings. This lack of correlation may be due to the inability of transcranial Doppler to differentiate between the relatively benign air emboli from the more damaging fat and atherosclerotic debris. This finding also brings into question whether microemboli are, in fact, the source of neurologic injury or whether other proposed mechanisms, such as systemic inflammation, ce-

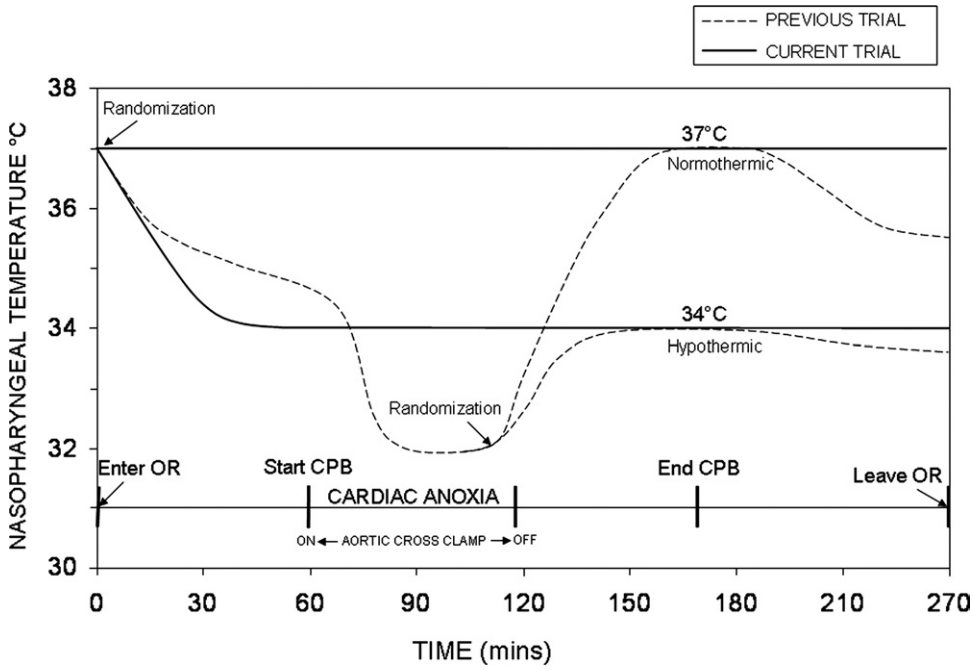

Figure 2. Schematic of intraoperative nasopharyngeal temperature in our previous study[12] and the current study. In the previous study, all patients were cooled to 32°C during CPB and then randomized to rewarming to 34°C or 37°C, whereas in the current study, cooling was initiated on entry into the operating room and sustained throughout the operative period. *OR,* Operating room; *CPB,* cardiopulmonary bypass.

rebral edema, and global hypoperfusion, are responsible. Other groups have also reported a lack of correlation between POCDs and cerebral ischemia detected by diffusion-weighted magnetic resonance imaging.[25] Last, a number of studies have identified various preoperative patient characteristics (eg, age, education level, serum creatinine level, left ventricular function, and other variables) that are predictive of postoperative cognitive dysfunction.[26-28] It may be that the stress of surgery is not causal but merely unmasks preexisting cerebrovascular disease and identifies the patients who are predisposed to future cognitive decline. POCDs may therefore be a marker of subtle preoperative cognitive changes and not evidence of intraoperative or perioperative cerebral injury. This suggestion would explain the disappearance of most deficits 3 months and 1 year after surgery with reappearance 5 years later.[3-5]

Conclusions

In patients undergoing coronary artery bypass surgery, sustained and mild intraoperative hypothermia (34°C) is safe but does not reduce the incidence of neurocognitive deficits. In the absence of cerebral hyperthermia and rewarming, there is no difference in outcome between sustained mild hypothermia and normothermia.

We thank Medivance (Louisville, Colo) for providing the thermal control system and pads, and we acknowledge the expert assistance of Carmen Altoft, RN, Sharon Finlay, RN, Lynn Gagné, RN, Linda Vasudev, PhD, and Denyse Winch, RN.

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Discussion

Dr J. Hammon *(Winston-Salem, NC)*: I congratulate Dr Boodhwani and his coworkers on an excellent randomized prospective study, and thanks again for sending me the article and the slides in advance. Our group and others have admired the work of Dr Nathan and people like yourself who have done careful randomized studies evaluating hypothermia as a neuroprotective adjunct to surgery. The previous article that you referred to was what I would call a landmark study in that as a result of your publication, many groups, including ours, stopped doing active rewarming in the operating room, and I noticed you say in your article that this work served to validate that study.

In terms of the hypothesis that you gave at the beginning of your presentation, you stated that you wanted to validate the study and to actually examine the effects of hypothermia without the effects of rewarming. Tell me how you arrived at this and why you used the water jacket on the hypothermic patients, given that the pump temperature was exactly the same as the temperature that you were aiming for (34.5°C) and should have maintained the brain at that temperature?

Dr Boodhwani: Thank you for your positive comments. First of all, the reason for the confirmatory study was the fact that the first study was confounded by the effect of rewarming. Although hyperthermia was avoided in both studies, it was impossible in the first study to separate the potential harmful effect of rewarming in the normothermic group from the potential beneficial effect of hypothermia in the hypothermic group, and therefore we wanted to conduct a study in which pure hypothermia was the only intervention. The best way to achieve that without relying on the CPB machine, for which you would have to first cannulate the aorta and venous system and then go on-pump and reduce the temperature, we chose to use an external method of reducing the temperature, so that by the time any possible emboli could occur to the cerebral vasculature, our intervention was already in place, which was what we demonstrated in this study.

Dr Hammon: I think it was admirable for you to show that an operation like this can be carried out with a 3-month neurocognitive deficit rate of less than 10%, which mirrors some of our own studies. I think that should be the standard that all of us aspire to.

I would have to say that when you reduce neurocognitive dysfunction rates to that level, determining a statistically significant difference between 2 groups becomes difficult, even with your 40% rate at the end of discharge, when most of the older rates were in the 60% to 70% range. When we calculate the statistical power with our techniques, at least 400 patients would be required to be able to tell a difference if you had a deficit rate of 40% at discharge. Did you do a statistical power calculation?

Dr Boodhwani: Absolutely. This was reported in our article as well. The study was powered to detect a 25% reduction in cognitive deficits with the intervention, and that gave us a sample size of 300, and you will note that the study was stopped at 267 because of various logistic and funding issues. However, having done that prospectively, perhaps what is even more important is that at the time of discharge, the actual difference between the groups is only 4%. Although we were powered to detect a significant difference, the actual treatment effect is quite low.

Dr Hammon: I think it is very important for you to show that last slide and to emphasize in the article that what most of us think is the real problem in terms of reducing temperature in patients would be active rewarming. For many perfusionists around the country, and if you look at the AmSECT meetings that I go to regularly, the standard procedure 10 years ago was to cool the patient to 28°C and then rewarm the patient to 37°C in approximately 10 or 15 minutes, which means the water bath on the pump has to be set to 38.5°C, and therein I think lies the rub; that is where the injury occurs and has been shown in animal experiments. So I think yours is a very valuable contribution. I think you have to say that hypothermia is very important for our patients; I don't think we can downgrade that, but active rewarming is very dangerous. Thank you.

Dr Boodhwani: Thank you, Dr Hammon. I would just like to echo those comments. One of the things that this study reemphasizes is that surgeons do need to pay attention to the way in which temperature is managed, and in particular avoid rewarming. One caveat, however, is that the study was not powered to demonstrate an effect of hypothermia on strokes. Certainly, you would need a study with thousands of patients to demonstrate that, and we can't exclude a beneficial effect of hypothermia in the setting where there is a high suspicion for clinical stroke. However, with respect to cognitive deficits, certainly our studies combined demonstrate that rewarming is harmful and that hypothermia in and of itself does not confer a significant benefit.

Dr G. Parr *(Morristown, NJ)*: I congratulate the authors on a well-designed and carried-out study. In your conclusions you note that the major problem may be the underlying cerebrovascular disease. If that were the case, you should note, as others have, that neurocognitive dysfunction is much more prevalent in the elderly patients, that is, you should have a correlation of age with neurocognitive dysfunction after 3 months. Did you note this in your patients?

Dr Boodhwani: That is correct. That is exactly what we noted, and actually we published this in *Circulation* in 2006 (*Circulation* 2006;114:I461-6) looking at predictors of neurocognitive deficits in a large cohort of patients, close to 500. We found that age was extremely predictive of neurocognitive deficits, and that the serum creatinine level, which likely represents an overall premorbid state, was also predictive of neurocognitive deficits.

Dr Parr: Secondarily, you excluded cerebral hypoperfusion, but you really don't have any data in this study on cerebral hypoperfusion.

Dr Boodhwani: Cerebral hypoperfusion is a hypothesis that has been maintained in the literature as a source of cognitive deficits. Our goal here was primarily based on the theory that POCDs occur from an ischemic/embolic cause. Certainly we took care to ensure that the blood pressure maintained during CPB was similar between groups and maintained as per guidelines, but we didn't specifically control for that.

Dr R. Griepp *(New York, NY)*: Just a follow-up question on that. You state that your pressures were the same. So were the flows the same, your CPB flows? I found it sort of interesting that you had exactly the same number of emboli in the hypothermic and normothermic groups. One would assume that that meant your flows were the same. Were they?

Dr Boodhwani: Yes, the flows were the same and maintained within a predefined interval throughout the study.

Dr Griepp: The pressure and the flows were the same both in the 34°C and in the 37°C groups?

Dr Boodhwani: That is correct.

Dr Griepp: That is unusual.

Dr Boodhwani: I would like to add that the hypothermic patients required more phenylephrine to maintain blood pressure.

Dr H. Nathan *(Ottawa, ON Canada)*: I thank the Society for the opportunity to present our results. I would like to take the liberty of interpreting the clinical relevance of our findings in the context of our research and the research of others. Our study and the work of Van Dijk and colleagues (*JAMA.* 2002;287:1405-12), comparing patients undergoing surgery with and without CPB, indicate that CPB is unlikely an important cause of cognitive deficits when conducted with the best possible technology and appropriate temperature management. The lack of effect of mild hypothermia in reducing the incidence of cognitive deficits suggests to us that the cause of these deficits is not ischemic. Mild hypothermia has, however, been shown to reduce ischemic brain injury in the laboratory and in patients with out-of-hospital cardiac arrest. It is possible, but not proven, that mild hypothermia may benefit patients at risk of cerebral ischemia in the operating room. I suggest that the 2 limbs of this trial offer useful management strategies. Patients at high risk of cerebrovascular events and those with carotid disease, high creatinine levels, or a previous stroke could be maintained at 34°C throughout the procedure, first using cooling pads at the beginning, a constant temperature on bypass, and then they could be rewarmed postbypass in the ICU. This strategy may provide neuroprotection to these patients without increasing operating room time by attempting to rewarm on CPB. We have shown that it is safe to take most patients to 34°C. On the other hand, if the patient is not at high risk of cerebrovascular injury, one could maintain the temperature at approximately 36°C to 37°C throughout the case, again avoiding rewarming on CPB and providing some of the benefits of normothermia.

I concur with Dr Hammon that it is important to avoid rewarming on CPB, which even when done cautiously, as in our first study, seems to be related to cerebral injury.

Dr P. Kurlansky *(Miami, Fla)*: Given that rewarming is apparently damaging, I was wondering if you had any idea as to the basic science mechanism, if it has to do with the solubility of gas at different temperatures and coming out of solution? What is the exact problem?

Do you have any advice for those situations, deep hypothermia for aortic surgery, in which rewarming is unavoidable? Is there any technique of rewarming that might be more protective against the cerebral injury that you have found?

Dr Boodhwani: From a basic science point of view, a number of different mechanisms have been implicated in the beneficial effects of hypothermia and detrimental effects of rewarming, and they range anywhere from the onset of cerebral injury to excitatory transmitter release, all the way down to the cellular events leading to neuronal death, and any of those mechanisms might be at play. Certainly I think intuitively it makes sense to extend the period of rewarming over a longer period of time and to minimize the rate of increase in temperature over a short period of time in an effort to avoid reperfusion injury.

Dr C. Feindel *(Toronto, Ontario, Canada)*: That was an excellent presentation. Just for interest's sake, can we just have a quick show of hands to see who uses standard rewarming techniques? (Show of hands.) And those who use this modified technique? The minority it seems. Thank you.

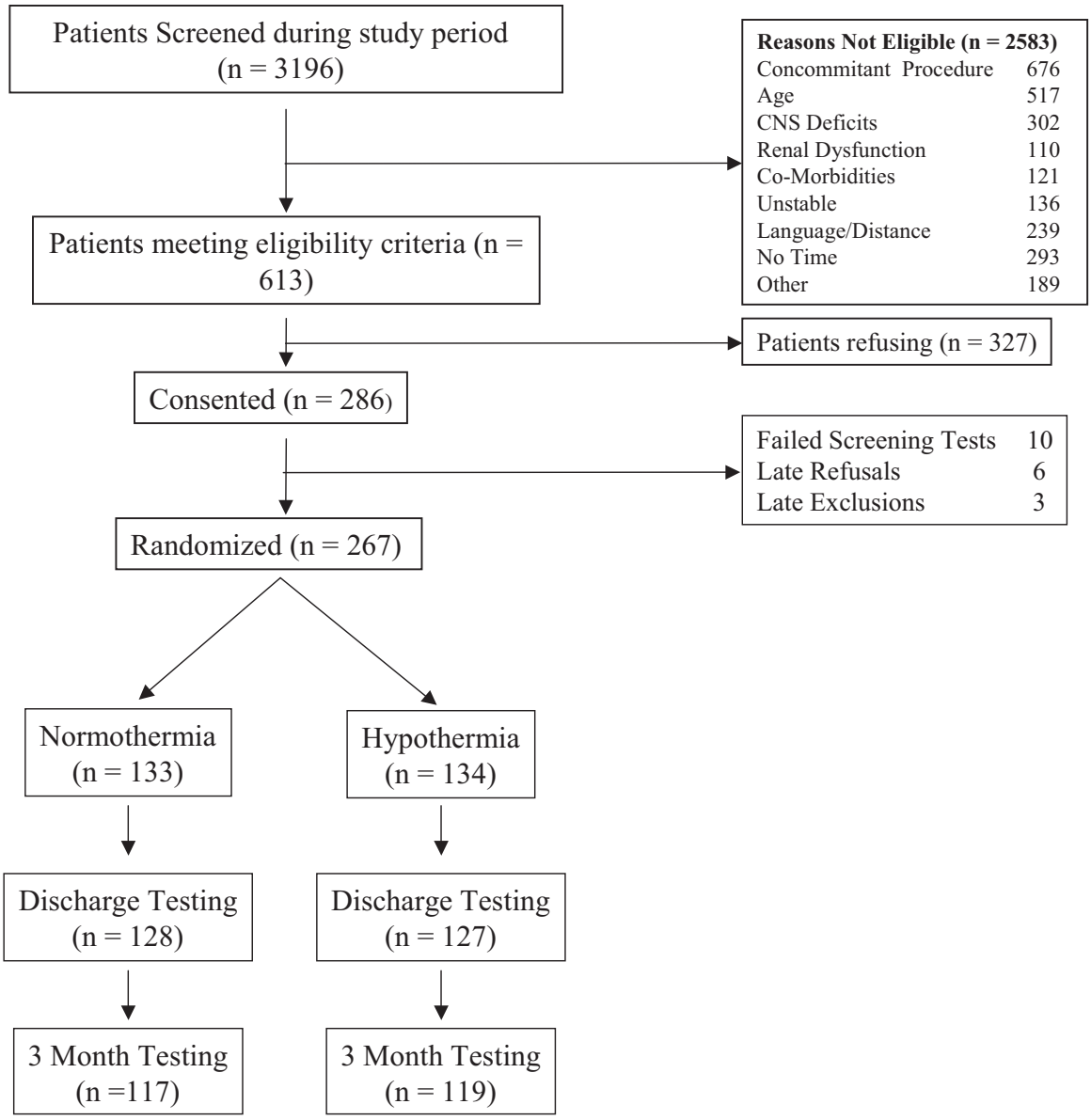

Figure E1. Patient screening and enrollment. *CNS,* Central nervous system.